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Primary Malignant Melanoma of the Esophagus

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A 48-year-old woman presented with a 6-month history of dysphagia, often associated with retrosternal chest pain. Upper endoscopy revealed an unusual pigmented lesion within the middle portion of the esophagus, and multiple biopsies were obtained. The histopathology and immunohistochemical profile of the tissue specimens were diagnostic of malignant melanoma. A thorough clinical and radiographic evaluation was performed, providing no additional findings or alternative primary source. Of approximately 11,500 melanoma patients entered in the Duke University melanoma database since 1970, this represents the only case of primary esophageal melanoma. The case is described and a review of the literature is presented. *J. Surg. Oncol. 1997;66:201–206.*

KEY WORDS: **malignant melanoma; esophagus; primary neoplasm**

INTRODUCTION

Primary malignant melanoma arising in the esophagus is an extremely rare lesion, with slightly more than 100 cases reported in the world literature to date [1–5]. Its manifestations are very similar to those of epithelial esophageal carcinomas and are usually of short duration before diagnosis. Although current radiologic modalities are adequate in identifying and localizing the tumors, the diagnosis must be established through histologic examination. The treatment of choice is radical surgical resection, with little indication for adjuvant therapy, except in a palliative role. Despite intervention, this diagnosis portends a poor prognosis, with very few patients living beyond 5 years.

Despite our growing understanding of this tumor, little is known about its biologic characteristics and natural history. The histologic criteria previously defined to aid in its primary localization are controversial and the distinction between primary and secondary disease remains challenging.

CASE REPORT

A 48-year-old Celtic woman presented with dysphagia and intermittent retrosternal chest pain of 6 months' duration. She reported the sensation of food lodging in her lower mid-sternal region. This sensation, often accompanied by pain, occurred most commonly while she was eating or shortly thereafter, and could be relieved somewhat by standing erect or ambulating. She denied the presence of worrisome cutaneous lesions, or of moles that had spontaneously disappeared in the recent past. She had no visual complaints.

Physical examination was unremarkable, with no primary cutaneous or ocular lesions encountered. There was no unusual lymphadenopathy. Routine blood work, chest

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X-ray, electrocardiogram, and echocardiogram showed no significant abnormalities. Esophagogastroduodenoscopy revealed an unusual-appearing, bluish pigmented mass within the esophagus extending from 28 to 32 cm from the oral incisors. The mass measured 1.5 cm in width and was oriented along the longitudinal axis of the esophagus. Several areas of ulceration were noted. Biopsies were obtained, revealing a dense proliferation of epithelioid and spindle-shaped cells within the connective tissue beneath the epithelium. Most of these cells contained brown melanin pigment and were positive for both S-100 protein and HMB-45 antigen by immunohistochemical analysis. Based on these results, the diagnosis of melanoma was established.

Upper GI series confirmed the presence of a 5 × 2 cm mass in the midesophagus (Fig. 1). There was narrowing of the esophagus, with a residual lumen measuring approximately 15 mm. Thoracic computed tomographic scan with contrast revealed some fullness at the level of the midthoracic esophagus, just below the carina, with no involvement of adjacent structures. No mediastinal or hilar adenopathy was seen and no pulmonary lesions were identified. Endoscopic ultrasound demonstrated a T1 lesion, with no suspicious periesophageal lymph nodes identified (Fig. 2). Computed tomographic scans of the head and abdomen showed no evidence of metastatic disease.

An Ivor-Lewis esophagogastrectomy was performed with macroscopically complete excision of the lesion. The patient's convalescence was remarkable only for a bout of aspiration pneumonia, diagnosed on postoperative day 6. She recovered well with appropriate therapy and was discharged home on the 16th postoperative day. Upon returning to the clinic, she complained of some mild dysphagia for solid foods. Stenosis from scarring was deemed responsible and she underwent endoscopic dilation of the site. Esophageal biopsies obtained at that time were negative for recurrent disease. At the present time, the patient is approximately 7 months out from surgery and is doing well, with no evidence for recurrence of the melanoma.

Fig. 1. Upper GI series reveals midesophageal mass.

Pathology

Gross. The surgical specimen consisted of a segment of esophagus (Fig. 3) measuring 9 cm in length. A dark brown, irregularly ovoid nodule was noted, measuring approximately 3 × 2.5 × 1.3 cm. It was located approximately 5.7 cm and 1 cm from the esophageal and gastric margins of resection, respectively. Upon sectioning, the nodule was composed of gray-brown tissue measuring 1.3 cm in greatest thickness and confined to the mucosa and submucosa, with no gross muscular involvement. No other focal lesions were found on further sectioning.

Microscopic. Sections revealed a portion of the esophageal wall with a large nodule present within the submucosa (Fig. 4). The nodule was composed of large epithelioid and spindle cells with hyperchromatic nuclei and prominent nucleoli (Fig. 5). The presence of melanin pigment was confirmed. At the periphery of the nodule, melanophages could be seen (Fig. 6), along with an area of fibrosis, consistent with changes of regression. An intraepithelial component was not identified and the muscularis was not involved by tumor cells. The surgical and mucosal margins were negative for tumor. Three mediastinal lymph nodes were uninvolved by melanoma. A complete search for another primary melanoma was negative and, despite the absence of a junctional component adjacent to the tumor mass, the diagnosis of primary melanoma of the esophagus was favored.

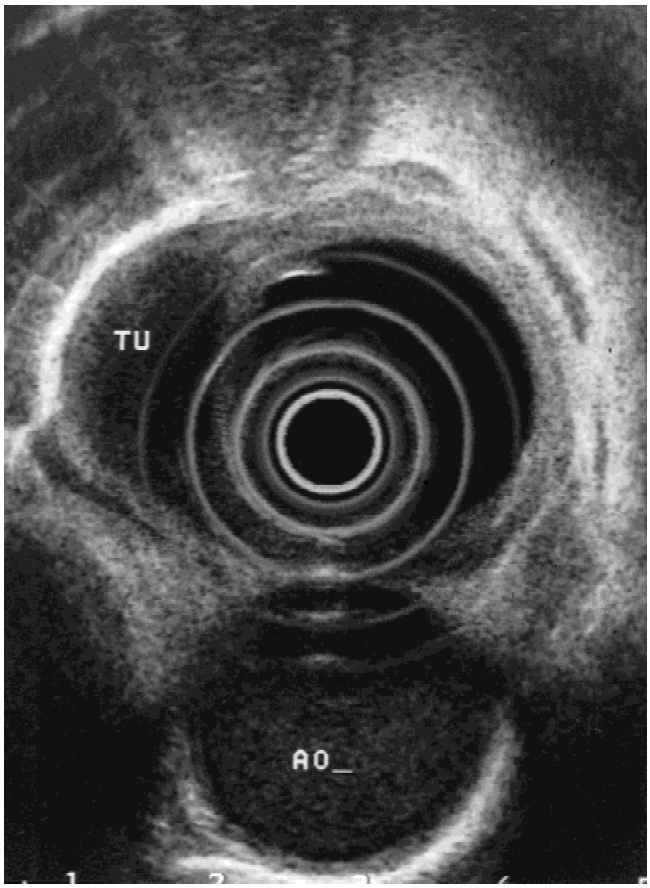

Fig. 2. Upper endoscopy with ultrasound demonstrates T1 tumor of the esophagus (TU) at 29 cm. There are no suspicious periesophageal lymph nodes. The descending aorta (AO) is seen posteriorly.

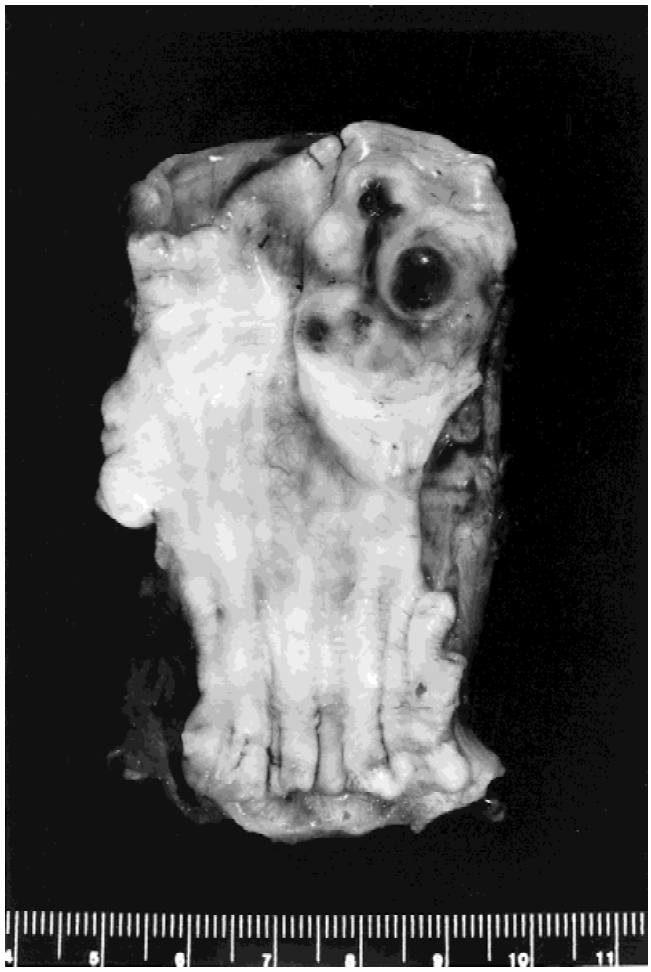

Fig. 3. Surgical specimen consisting of a 9-cm segment of the mid-esophagus. The specimen was opened longitudinally, revealing the pigmented mass.

DISCUSSION

Primary esophageal melanoma was first described by Baur in 1906 [6]. It was not until 1952, however, that the first case was reported by Garfinkle and Cahan [7]. This report was received with great skepticism until 1962, when de la Pava et al. established the presence of normal melanocytes in 4 of every 100 human esophagi examined at autopsy [8]. It is believed that these melanocytes migrate from the neural crest to the esophagus during embryogenesis in the same way they migrate to the skin and other organs [9]. Prior to this discovery, all esophageal melanomas had simply been classified as metastatic disease.

Malignant melanoma of the esophagus is an extremely rare tumor. In 1973, Turnbull et al. [10] reported that, from 1926 to 1968, only 2 melanomas (0.1%) were found out of 1,918 malignant tumors of the esophagus seen at Memorial Hospital of New York. Later, McCormack and his colleagues [11] discovered only 5 melanomas (0.2%) out of 2,100 cases of esophageal carcinoma reviewed. Lastly, Suzuki and Nagayo [12] studied 11,932 esophageal malignant tumors from surgical specimens and 4,995 from autopsied materials in Japan, uncovering 16 (0.1%) and 7 (0.14%) melanomas from each group, respectively. Conversely, the esophagus is a rare location for the occurrence of melanoma. Barely 15% of all melanomas are encountered in noncutaneous sites [13], with a meager 0.5% of these arising in the esophagus [14].

As the number of case reports on the subject continues to grow, a consistent clinical picture is emerging. The affected patients are usually in their fifth decade or older, with a mean age of 59.6 years [1]. There is only one reported case in a child, that of a 7-year-old boy described by Basque et al. [15]. These tumors seem to occur most often in men, with a male-to-female ratio of approximately 2:1 [1,16], and Caucasians are almost exclusively affected. The exact cell of origin of these tumors remains elusive, although some suggest that they may arise within ectopic nests of melanoblasts that migrate to the esophagus during development. The first case of esophageal melanoma in the setting of melanosis of the entire esophagus was reported by Piccone et al. in 1970

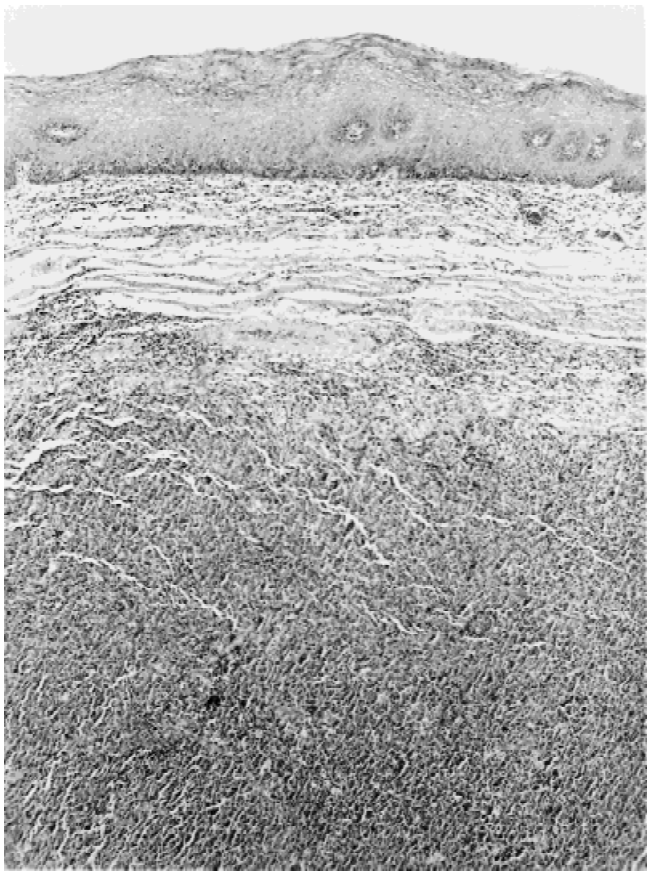

Fig. 4. A nodule comprised of atypical cells can be seen within the submucosa. Note that the overlying stratified squamous epithelium is uninvolved. (Hematoxylin and eosin stain; original magnification, ×52.)

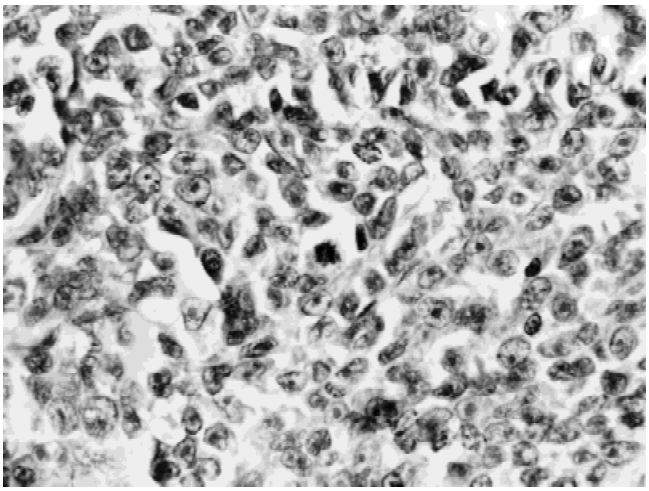

Fig. 5. Poorly cohesive, pleomorphic neoplastic cells with hyperchromatic nuclei and prominent nucleoli. Note the mitotic figure (center). (Hematoxylin and eosin stain; original magnification, ×680.)

[17] and several authors have described an association with partial melanosis [9,18]. Many consider that melanosis could be a predisposing factor for esophageal melanoma, because it is found in approximately 25% of these patients [18,19].

At presentation, the patients most commonly complain of dysphagia, vague retrosternal pain, and weight loss, not unlike the presenting symptoms associated with epithelial tumors of the esophagus [1,20]. Epigastric discomfort, regurgitation, chest pain, and vomiting are also reported, although less frequently. Hemoptysis and hematemesis are rarely present. In most cases, the symptoms exist only a few months before diagnosis [21]. Approximately 90% of the tumors are located in the lower two-thirds of the esophagus. Their tendency to be large, intraluminal, polypoid, and irregular in appearance, renders them easy to delineate with a barium swallow. Upper endoscopy is also helpful in demonstrating and localizing these lesions, usually revealing a polypoid and pigmented mass in a majority of the cases [20]. Approximately 50% of these patients have some form of metastatic disease at presentation [3], underlining the extensive nature of the disease when patients first seek help for their symptoms.

Despite the characteristic findings associated with esophageal melanoma, its clinical diagnosis is not feasible. The signs, symptoms, and radiographic studies described above remain nonspecific for this tumor, and the final diagnosis must be established histologically. According to the original criteria defined by Allen and Spitz [22], the tumor is considered to be primary melanoma when (1) it manifests the characteristic structure of melanoma and contains melanin pigment, (2) melanocytes can be found in the adjacent epithelium, (3) the tumor is polypoid, and (4) it originates from an area of junctional activity within the squamous epithelium. Although some authors agree that the presence of junctional changes at the margins of a polypoid melanoma is required as proof of primary origin [22,23], others believe that this junctional component could be obliterated by aggressive tumor growth in some cases [24–26]. Sixty percent of the esophageal melanomas described by Kreuser [27] failed to fulfill this criterion, and he relied instead on the presence of concomitant benign melanocytosis as evidence of their primary nature. It is well known that some malignant melanomas arise purely intradermally from a congenital nevus or blue nevus [28–30].

Frequently, the histopathologic diagnosis is not established until after curative resection is performed. Endoscopic biopsy yields diagnostic specimens only 50% of the time [13]. Cytologic examination of washings and brushings is also variably useful. Once melanoma is discovered in biopsy material, however, immunohistochemistry and electron microscopy help distinguish between primary and metastatic disease [18,31]. Regardless of the information available, a thorough history and physical examination remain invaluable in excluding the presence of a cutaneous or ocular primary tumor.

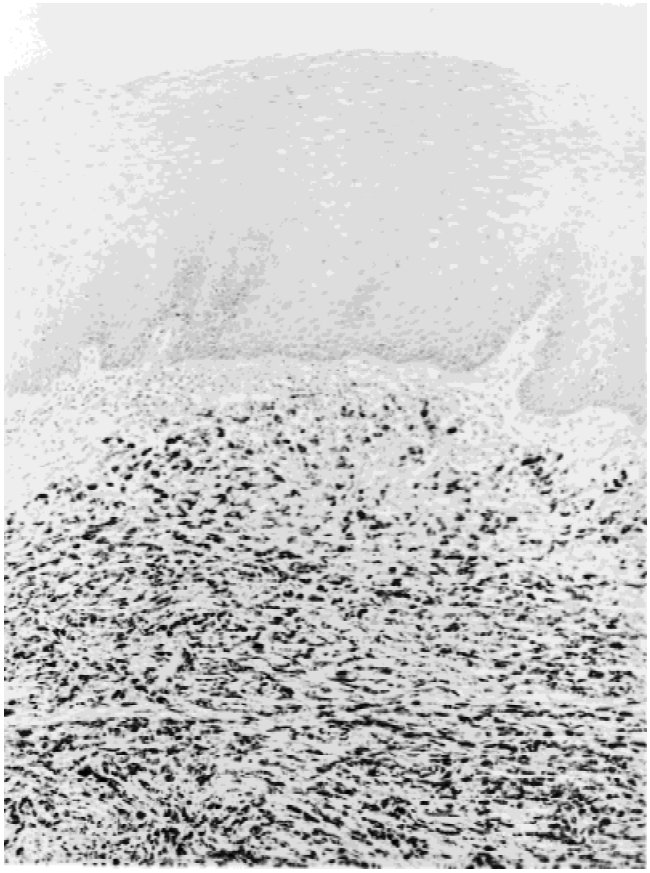

Fig. 6. Zone of regression with prominent melanophages. (Hematoxylin and eosin stain; original magnification, ×100.)

Primary esophageal melanomas display pathologic features that are fairly consistent. Grossly, these tumors tend to be large, polypoid, stenosing, and focally ulcerated. Eighty-five percent are pigmented, although they may range in color from white to brown-black. Despite their bulkiness, they are usually covered by a layer of intact squamous mucosa. When examined histologically or cytologically, they are very similar to their cutaneous counterparts. Cellular pleomorphism is considerable, with variations in cell size and shape seen between different patients, as well as within given tumors. Microscopic pigmentation is present in 9 of 10 specimens. The cells are often organized in ''nests'' or alveolar arrangements. Growth occurs mainly in the submucosa, which often masks the true extent of these tumors on gross examination. The pattern is most consistent with a ''pushing'' rather than an infiltration of the deep margin, and the overlying squamous mucosa is seldom invaded. As seen with other mucosal melanomas, the radial growth phase pattern is lentiginous.

Both hematogenic and lymphogenic metastases are common. In a series of 45 postmortem examinations, it was found that the most common site of metastases was the liver (31%), followed by the mediastinum and mediastinal lymph nodes (29%), the lung (17.7%), and the brain (13.2%) [1]. Metastases to other intra-abdominal organs and to the skeleton were also noted, but were less common. Twenty-two percent of the patients had no metastases present at the time of death. Of note, melanoma has a relatively high incidence of cardiac metastases [32] and a rare isolated case of a left atrial metastasis in the setting of a primary esophageal melanoma was recently reported [33].

The prognosis for primary esophageal melanoma is extremely poor. The mean survival after diagnosis is 13.4 months with a 5-year survival of 4.2% [1]. This is most likely due to the advanced state of these tumors at the time of diagnosis. Among 110 cases reviewed, it was found that 31% were only treated symptomatically, either because of unresectable locally advanced disease, widespread metastases, or the patient's poor state of health [1]. To our knowledge, only two reports exist of patients living 10 or more years [12,34]. In each case, the patients had been treated with surgery only. Radical resection increases the mean survival over local excision [35], with a reported postoperative mortality of 0–6.2% [35]. This resection should be performed with concomitant restoration of gastrointestinal continuity and remains the treatment of choice, provided the patient's associated morbidity risks are acceptable [12,19,35].

Although there is an isolated report of a long-term survivor treated with radiotherapy alone [11], melanoma is generally considered to be a radioresistant tumor, and no clear role exists for radiotherapy in primary management. In some cases in which surgery is not feasible, the use of external beam and intracavitary radiotherapy may have a palliative role [2]. Both radiotherapy and chemotherapy, with single or combined agents, have been used to treat esophageal melanoma in the past. Unfortunately, neither of them has been shown to improve survival for these patients [26]. At the present time, all adjuvant modalities have been relinquished to palliative roles.

CONCLUSIONS

We have presented a case of primary melanoma of the esophagus. The characteristic clinical, radiographic, and histologic features are included in this description. The histologic criteria outlined by Allen and Spitz [22], and later supported by Raven and Dawson [23], serve as important guidelines in the diagnosis of this rare tumor. Many believe, however, that aggressive tumor growth could obliterate the zone of junctional activity. Our patient underwent a thorough clinical and radiographic work-up, which failed to reveal either an alternative primary site or additional metastatic foci. This evidence, along with the histologic characteristics of the tumor, led to the diagnosis of primary melanoma of the esophagus.

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